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Causes of AKI in Cirrhosis

Case Background

A 68-year-old-male is brought to the emergency department by his wife and son because of the acute onset of vomiting and altered mental status for the past 48 hours. The patient's medical history includes cirrhosis complicated by hepatic encephalopathy, esophageal varices, and ascites requiring therapeutic paracentesis once weekly. His outpatient medications include furosemide 40 mg oral daily, lactulose 20g/30 mL oral 3 times daily, nadolol 20 mg oral daily, pantoprazole 40 mg oral twice daily, and spironolactone 100 mg oral daily.

Physical examination shows the presence of moderate ascites and bilateral lower extremity edema, weight of 74.3 kg (dry weight 68 kg), blood pressure of 90/50 mmHg, heart rate of 123 beats/min, respiratory rate 20 breaths/minute, and temperature 98.1°F. Chest radiograph shows bilateral pleural effusions. Laboratory evaluation shows a serum creatinine of 3.2 mg/dL (most recent value 1.2 mg/dL), serum sodium of 121 mEq/L, total bilirubin 4.5 mg/dL, international normalized ratio (INR) of 2.4, and Model for End-Stage Liver Disease (MELD)-Na of 36.

Question 1

Which one of the following choices might have contributed to acute kidney injury in this patient?

A. Use of lactulose for treatment of hepatic encephalopathy
B. Small-volume paracentesis without albumin 25% replacement
C. Use of proton pump inhibitor for esophageal varices
D. Large-volume paracentesis without albumin 25% replacement

The correct answer is: D (Large-volume paracentesis without albumin 25% replacement)

Answer rationale:

- Patients with cirrhosis are susceptible to acute kidney injury (AKI) due to liver-related factors, such as the severity of disease or decompensating events, and/or the presence of concomitant comorbidities, including kidney disease, cardiomyopathy, hypertension, and diabetes.
- Nephrotoxins are a common modifiable risk factor for AKI. Nephrotoxins include nonsteroidal anti-inflammatory drugs (NSAIDs), aminoglycosides, nonspecific beta blockers, vasodilators, and diuretics, and the presence of volume depletion or infection.
- To prevent the development of AKI, albumin 20% to 25% replacement should be administered following a large-volume paracentesis (LVP), which is defined as >5L of ascites removed in a single session.
- Current guidelines do not recommend replacement with albumin following a small-volume paracentesis.
- As lactulose alters the acidity of gut flora and increases bowel movements, it may be used as a treatment for hepatic encephalopathy. It is considered safe for use in patients with cirrhosis and does not serve as a modifiable risk factor for the development of AKI.
- The use of proton pumps inhibitors is considered safe for use in patients with cirrhosis and does not represent as a risk factor for AKI.

Faculty Commentary

Dr. Subramanian: Just to expand upon this question further, I think this question addresses the important issue of any hypovolemic trigger being a driver for the development of HRS-AKI. So, as in this case, when somebody has a large-volume paracentesis and does not receive postparacentesis albumin replacement, that can further worsen renal perfusion because the underlying baseline hemodynamic profile is so tenuous because of a decreased central blood volume. And we'll talk about this more in other discussion.

Dr. Subramanian: Regarding question 1, the right answer is option D (large-volume paracentesis without albumin replacement). To expand upon this further, I think this question addresses the important issue of any hypovolemic trigger

being a driver for the development of hepatorenal syndrome-acute kidney injury (HRS-AKI). So, as in this case, when somebody has a large-volume paracentesis and does not receive postparacentesis albumin replacement, that can further worsen renal perfusion because the underlying baseline hemodynamic profile is so tenuous due to decreased central blood volume. We'll talk about this more in other discussion points. This speaks to the important concept of splanchnic vasodilation being a central driver of depleting the central blood volume because of a splanchnic shunt. The kidneys then are exquisitely sensitive to any hypovolemic challenge, such as a large-volume paracentesis that was described in this question.

The other point to be made using this question is when you think about acute AKI in cirrhosis, there are multiple potential triggers. If you look at the differential diagnosis, you have to think about renal azotemia, intrarenal causes, such as acute tubular necrosis (ATN), and especially the context of a septic trigger, like chronic liver failure. There is also postrenal etiology. So, the differential diagnosis is so broad, but HRS-AKI is a unique form of renal injury that can come into play in the setting of decompensated cirrhosis and portal hypertension.

Dr. Nanchal: There is a lot of talk about what and which type of fluid, whether albumin or crystalloid. I think this is one of the few areas where the data is very strong about administration of albumin as it pertains to postparacentesis secondary to dysfunction. So, the fluid of choice should be hyperoncotic albumin.

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Pathophysiology of HRS-AKI

Question 2

Which one of the following pathophysiologic changes is most likely associated with acute kidney injury in this 68-year-old man?

A. Upregulation of the parasympathetic nervous system leading to a reduction in heart rate and cardiac output
B. Increased production of proinflammatory molecules resulting in peripheral vasodilation and decreased vascular resistance
C. Upregulation of the renin-angiotensin-aldosterone system (RAAS) resulting in decreased sodium and water retention
D. Vasoconstriction within splanchnic circulation resulting in decreased portal blood flow

The correct answer is: B (Increased production of proinflammatory molecules results in peripheral vasodilation and decreased vascular resistance)

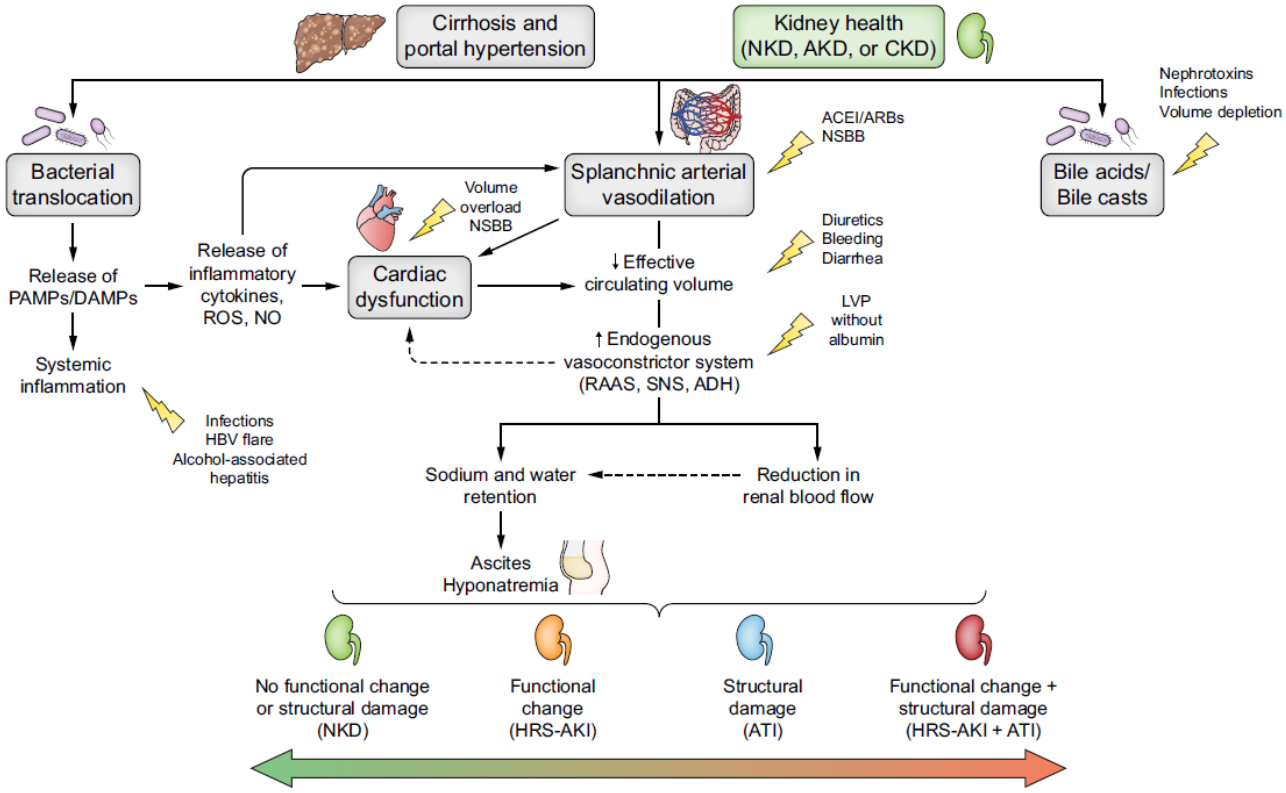
Answer rationale:

- Hepatorenal syndrome-acute kidney injury (HRS-AKI) is a form of renal failure occurring in patients with ascites and portal hypertension. The primary mechanism of HRS-AKI stems from decreased renal perfusion due to increased renal vasoconstriction.
- The development of portal hypertension is caused by increased intrahepatic resistance and splanchnic arterial vasodilation.
- Splanchnic vasodilation results in decreased circulating central blood volume, causing an upregulation of the renin-angiotensin-aldosterone system (RAAS), sympathetic nervous system (SNS), and antidiuretic hormone (ADH). The results are increased sodium and water retention, augmented cardiac output, and increased renal vasoconstriction.
- Systemic inflammation is often present in patients with cirrhosis, which can be associated with the release of pathogen-associated molecular patterns (PAMPs). PAMPs activate innate host immunity, causing an increased production of proinflammatory molecules.
- Proinflammatory molecules precipitate the release of cytokines and vasodilatory mediators to cause peripheral vasodilation and decreased vascular resistance.

Faculty Commentary

Dr. Subramanian: For question 2, the correct answer is option B (increased production of pro-inflammatory molecules resulting in peripheral vasodilation and decreased vascular resistance). We're talking about the pathophysiology of HRS-AKI; as option B states, one of the physiologies for the development of HRS-AKI is the increased production of proinflammatory molecules resulting in peripheral vasodilation and decreased systemic vascular resistance. I think the other important point to be made in this context is that, in addition to the peripheral vasodilation, there's also the other important driver of pathological splanchnic vasodilation in the setting of portal hypertension that induces a splanchnic shunt. These patients can actually have more than adequate cardiac output; in fact, they have supernormal cardiac output. But, because of the splanchnic shunt, they have abnormal shunting of the cardiac output into the splanchnic bed that, number 1, fuels portal hypertension. Importantly, the systemic manifestation of it is that you have a decreased central blood volume. The kidneys are exquisitely sensitive to this decreased central blood volume and therein lies the potential for the complication of HRS-AKI in this patient population.

As an extension of this point and in other questions is the central tenet of treating HRS-AKI using a splanchnic vasoconstrictor, like terlipressin. It speaks to proof of concept regarding the underlying pathophysiology that the root of the problem is pathologic splanchnic vasodilation that triggers the systemic derangements that lead to HRS-AKI.



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Diagnosis of HRS-AKI

Queston 3

Case Background (continued)

New information: After the initial laboratory panel, the patient was given 3 L of crystalloid solution, and a urinary catheter was placed. A second metabolic panel 8 hours later showed a serum sodium of 126 mEq/L and a serum creatinine of 3.1 mg/dL. Urine output is approximately 300 mL over the past 8 hours.

Which one of the following findings in this patient is specific for a diagnosis of hepatorenal syndrome-acute kidney injury?

A. Presence of cirrhosis with ascites
B. Increase in serum creatinine ≥0.3 mg/dL within 48 hours or ≥50% from baseline
C. Absence of improvement in serum creatinine or urine output following adequate volume resuscitation
D. Urine output <0.5 mL/kg/h for 12 hours

The correct answer is: A (Presence of cirrhosis with ascites)

Answer rationale:

- Societal guidelines define AKI based on an increase in serum creatinine (SCr) or decrease in urine output (UO) within a specified short period of time.
- The absence of SCr or UO improvement following adequate volume resuscitation is not a specific diagnostic criterion for HRS-AKI. This may indicate the need for additional clinical investigation in all forms of AKI.
- The 2021 Practice Guidance by the American Association for the Study of Liver Diseases (AASLD) and 2024 Acute Disease Quality Initiative (ADQI) and International Club of Ascites (ICA) mutually report the presence of cirrhosis with ascites as a specific diagnostic criterion for HRS-AKI.
- The 2024 ADQI/ICA joint multidisciplinary consensus meeting provides the following full diagnostic criteria for HRS-AKI:
    - Presence of cirrhosis with ascites
    - Increase in SCr $\geq$0.3 mg/dL within 48 hours or $\geq$50% from baseline value to have occurred within the prior 7 days and/or UO $\leq$0.5 mL/kg for $\geq$6 hours
    - Absence of improvement in SCr and/or UO within 24 hours following adequate volume resuscitation (when clinically indicated)
    - Absence of strong evidence for an alternative explanation as the primary cause of AKI

Faculty Commentary

Dr. Nanchal: Question 3 pertains to the diagnosis of HRS-AKI and the components that are necessary for the diagnosis. The correct answer for question 3 is option A (presence of cirrhosis with ascites). While AKI can occur, it can take many shapes and forms. HRS-AKI is purely a manifestation of decompensated cirrhosis; the presence of cirrhosis with ascites is, again, a marker of clinically significant portal hypertension and central to the development of HRS-AKI. A second point to be made is the evolution of the diagnosis of HRS-AKI. These definitions have been refined over the years with the final culmination in the 2024 joint Acute Disease Quality Initiative (ADQI) and the International Club of Ascites (ICA) consensus meeting. Specific criteria have been formulated on the presence of AKI in cirrhosis and urine output has been included. There have been new ones added to it. Contrary to the previous criteria of HRS-AKI, you now don't need 2 days of albumin resuscitation. It also gives leeway to the fact that HRS-AKI can coexist with other sorts of renal pathologies. For example, people with diabetes often have proteinuria and HRS-AKI, in which at least the physiology or even the syndrome can coexist. People have to be cognizant about those things. The third point to be made is that AKI depends on the definitions of baseline SCr. What constitutes a baseline SCr has been modified. It has become much more clear. So, these definitions of AKI in cirrhosis and HRS-AKI have come very harmonized with AKIN criteria of AKI.

Dr. Subramanian: Just to add to Dr. Nanchal's excellent points, I just want to reemphasize an important point he made that AKI, in the setting of cirrhosis, can be multifactorial. From a therapeutic standpoint, we often target multiple pathways in order to improve the AKI, understanding that it could have a multifactorial etiology.

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Reversal of HRS-AKI

Case Background (continued)

New information: This 68-year-old man meets diagnostic criteria for HRS-AKI and is transferred to the floor for treatment. The medical team discusses therapy for this patient.

Question 4

Which of the following mechanisms of action would target the specific pathophysiologic abnormalities exhibited by the signs/symptoms observed in this patient?

A. Intravascular volume repletion
B. Splanchnic vasoconstriction
C. Alpha-adrenergic antagonism
D. Positive inotrope

The correct answer is: B (Splanchnic vasoconstriction)

Answer rationale:

- As splanchnic vasodilation is a source for the upregulation of ADH and RAAS and SNS systems, vasoconstrictive effects within the splanchnic vasculature target a specific pathophysiologic abnormality in HRS-AKI.
- Intravascular volume should be assessed in HRS-AKI. If clinical and hemodynamic markers are consistent with intravascular volume depletion, fluid resuscitation should be completed within the first 24 hours of diagnosis with a reassessment of response. If markers are consistent with euvolemia or volume overload, intravascular volume repletion would not be appropriate and may lead to increased fluid accumulation.
- As the release of proinflammatory mediators causes peripheral vasodilation in HRS-AKI, use of an alpha-adrenergic antagonist would result in increased vasodilation and not serve as an optimal treatment of HRS-AKI.
- In decompensated cirrhosis, cardiac output may be augmented to compensate for peripheral vasodilation and renal hypoperfusion. While use of a positive inotrope agent would provide increased cardiac output, it does not serve as a targeted treatment specific to pathophysiologic abnormalities in HRS-AKI.

Faculty Commentary

Dr. Nanchal: Question 4 pertains to therapy for HRS-AKI; the correct answer is choice B, which is splanchnic vasoconstriction. As we have elucidated in the previous questions, the pathophysiological derangements of HRS-AKI include intense splanchnic vasoconstriction. In fact, the blood volume and the cardiac output might be supernormal. But, because of the splanchnic shunt and vasodilation, there is low central blood and circulating volume. The kidneys get hyper-perfused and that leads to a counter-regulatory, up-regulation of hormones that are central to the pathophysiology of HRS-AKI. This targets the reversal of splanchnic vasoconstriction; by constricting the splanchnic beds, the blood volume that is in the splanchnic circulation can be redirected into the central circulation and the kidneys can be perfused much better. That is the central role of using vasoconstrictor therapy in attempt to reverse HRS-AKI.

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Treatment Options for HRS-AKI

Question 5

Which one of the following is an appropriate treatment option for this 68-year-old man?

A. Nonselective beta blockers
B. Albumin monotherapy
C. Octreotide monotherapy
D. Vasoconstrictor therapy

The correct answer is: D (Vasoconstrictor therapy)

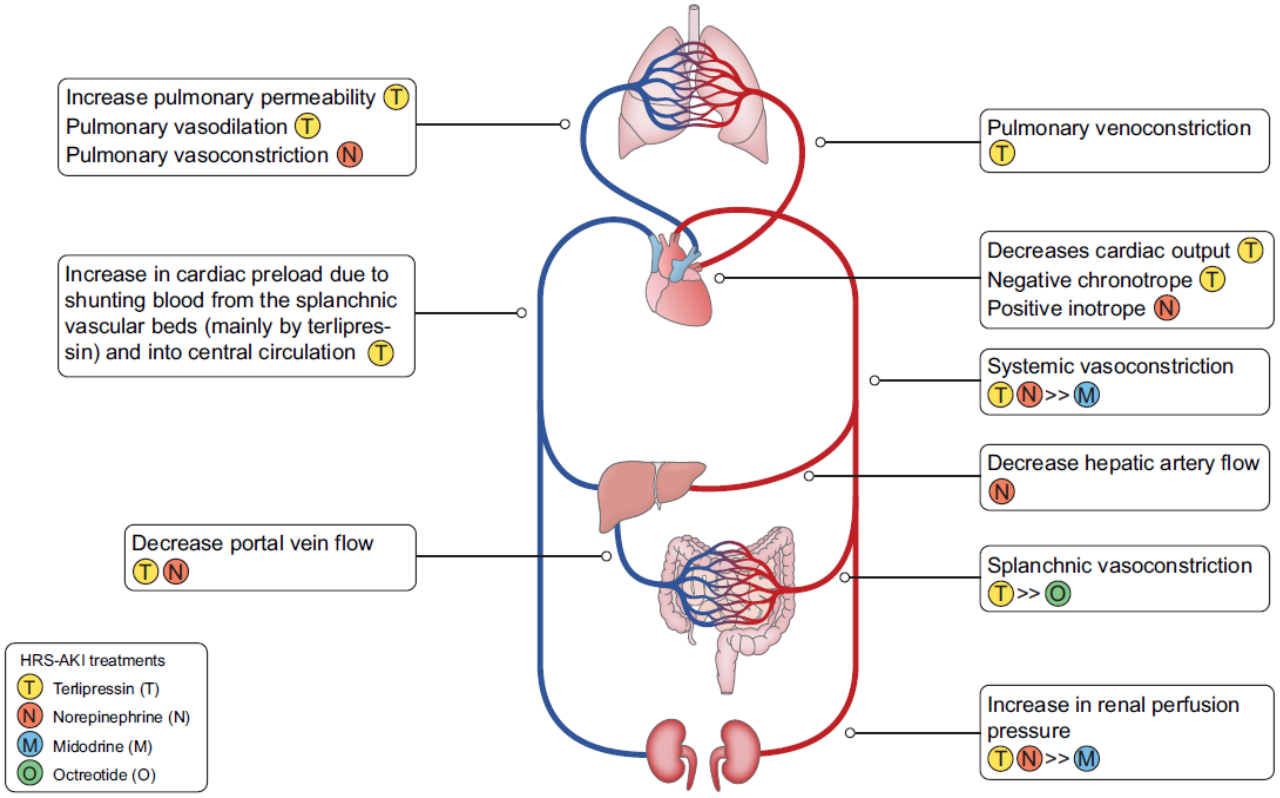
Answer rationale:

- The use of nonselective beta blockers may be used in patients with cirrhosis for the prevention of variceal bleeding. This medication class causes splanchnic arterial vasoconstriction, which decreases portal blood flow, as well as reduces arterial blood pressure and cardiac output. These mechanisms serve as a risk factor for decreased renal perfusion and AKI and may be considered for discontinuation upon the diagnosis of HRS-AKI.
- Based on the assessment of intravascular volume, the use of albumin for fluid resuscitation may or may not be indicated in the treatment of HRS-AKI.
- Octreotide provides splanchnic vasoconstriction, resulting in a modest increase in renal perfusion. Treatment with octreotide monotherapy is not optimal as it does not provide systemic effects. Current guidelines recommend treatment with midodrine and octreotide to provide systemic and splanchnic vasoconstrictive effects.
- Vasoconstrictor therapy provides multiple mechanisms to treat the pathophysiologic abnormalities of HRS-AKI, including systematic vasoconstriction, decreased hepatic artery and portal vein flow, splanchnic vasoconstriction,

and increased renal perfusion pressure. This class of medications would be an appropriate treatment option for HRS-AKI.

Faculty Commentary

Dr. Nanchal: The next question is a continuation of the previous one on appropriateness of treatment of HRS-AKI. Again, as we had mentioned before, the idea here is to attempt to reverse the vasodilation that is occurring in the splanchnic bed. That is done by vasoconstrictor therapy. Now, vasoconstrictor therapy comes in a variety of flavors. One could use terlipressin, which is preferred, norepinephrine, or a combination of midodrine and octreotide. But the central tenet here is to use vasoconstrictor therapy, preferentially one that targets the splanchnic bed. Now, a couple more points to be made here are that often people are on beta blockers because of clinically significant portal hypertension. While beta blockers do vasoconstrict the splanchnic bed, they can also cause decrements in cardiac output. Recall that the kidneys in HRS-AKI are sensing low cardiac output and one does not want to have any derangements in cardiac output. So, therapies that decrease cardiac output should be discontinued. A third point to be made is obviously volume status. Often, we will use a combination of albumin and vasoconstrictor therapy, but the administration of albumin should be done with caution and very careful assessment of volume status, especially with terlipressin, which has an associated risk of pulmonary edema. One of the mechanisms of pulmonary edema might be the creation of volume overload by giving inappropriate resuscitation with albumin therapy.



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Guideline-Directed Treatment of HRS-AKI

Question 6

Which one of the following vasoconstrictor therapies would be most appropriate for this patient?

A. Vasopressin continuous infusion
B. Albumin 25% 50 g/day for 3 days
C. Midodrine 15 mg oral every 8 hours
D. Terlipressin 1 mg intravenous bolus every 6 hours in combination with albumin 25% 75 g/day

The correct answer is: D (Terlipressin 1 mg intravenous bolus every 6 hours in combination with albumin 25% 75 g/day)

Answer rationale:

- Vasopressin is a hormone analog resulting in increased blood pressure through increased extracellular fluid retention. Increased sodium and fluid retention may be present upon the diagnosis of a patient with HRS-AKI due to the upregulation of ADH in the disease process.
- Based on the assessment of intravascular volume, the use of albumin for fluid resuscitation may or may not be indicated in the treatment of HRS-AKI. Albumin is not recommended as a monotherapy treatment because it does not target specific pathophysiologic abnormalities of HRS-AKI.
- Midodrine causes systemic vasoconstriction but provides a weak increase in blood pressure. Treatment with midodrine monotherapy is not optimal as it does not provide effects within the splanchnic vasculature. Current guidelines recommend treatment with midodrine and octreotide to provide systemic and splanchnic vasoconstrictive effects.
- The 2021 AASLD practice guidance and 2024 ADQI/ICA consensus meeting recommend first-line initiation of vasoconstrictor therapy, including terlipressin as the preferred agent, to be used in combination with albumin.
- Based on the patient case, a regimen of terlipressin 1 mg intravenous bolus every 6 hours in combination with albumin 25% 75 g/day is consistent with guideline-directed treatment of HRS-AKI.
- 2021 AASLD and 2024 ADQI/ICA guidelines recommend the use of norepinephrine for the treatment of HRS-AKI if terlipressin is not available.

Faculty Commentary

Dr. Subramanian: Question 6 addresses evidence-based guidelines for the treatment of HRS-AKI. The correct answer is option D (terlipressin 1 mg intravenous bolus every 6 hours in combination with albumin 25% 75g/day). Just to discuss this issue further, terlipressin has been standard of care for more than a decade in Europe for the treatment of HRS-AKI and has relatively recently been approved by the Food and Drug Administration (FDA) for its use in the United States (US). This speaks to the superiority of terlipressin with respect to midodrine and octreotide in particular as far as reversal of HRS-AKI because it is a more potent splanchnic vasoconstrictor. So, that I think underlines that terlipressin has been shown to be superior in multiple randomized controlled trials and even observational studies with respect to other options. The other point I'd like to make is the importance of coadministration of albumin. An important point to be noted

is that clinical trials and observational studies have shown that coadministration of albumin enhances the efficacy of terlipressin with respect to reversing HRS-AKI. There's a synergistic effect when you couple the terlipressin with albumin.

Dr. Nanchal: Ram, the point is well-taken about the synergistic effect of albumin and terlipressin. In your clinical practice, do you ever see the overuse of albumin while people are giving terlipressin?

Dr. Subramanian: That's a great question. I think this is evolving concept, especially going back to the point which you made earlier about a potential risk of hydrostatic pulmonary edema as you co-administer albumin for X number of days. I think there needs to be some clinical reassessment as you coadminister albumin on a daily basis to make sure that you're not developing intravascular volume overload. The other point to be made, and I'm glad you brought up this issue, is that the dosing of albumin is lower with coadministration; it's about 40 grams a day (g/d) as compared to what you do when you initially challenge prevasoconstrictor therapy to differentiate from prerenal azotemia. Typically, the recommendations are almost 1-1.5 grams per kilogram per day (g/kg/d), so that's 25g every 6 hours or 100 g/d of albumin. I think an important take-home message, as well, is when you coadminister, the albumin dose should be lower than what you do for the initial challenge prevasoconstrictor therapy.

Actually, your point brought up another issue on the use of norepinephrine. That's an important point to share with the audience. Especially in the intensive care unit (ICU) setting when you have a central line, there is data that norepinephrine efficacy is comparable to terlipressin when you increase the mean arterial pressure (MAP) by 10 millimeters of mercury (mmHg) above baseline. Typically, it's shooting for a MAP of 75 mmHg. That strategy, again with judicious use of albumin, has been shown to be equally efficacious with respect to HRS reversal similar to terlipressin.

Dr. Nanchal: The point's well-taken. How often do you use midodrine and octreotide in your clinical practice now?

Dr. Subramanian: That's another great question. We'll get to this later, but if you have a contraindication to terlipressin and don't have a central line, you don't have the luxury of norepinephrine. I think, in those situations, midodrine and octreotide still has a role. But if you have somebody with hypoxemia, preexisting pulmonary edema, or advanced grade acute-on-chronic liver failure (ACLF), norepinephrine may find its way there. Some of those potential barriers to terlipressin may make me think about reverting back to midodrine and octreotide because of the absence of other options.

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Monitoring of Vasoconstrictor Treatment in HRS-AKI

Question 7

Which one of the following should be done before starting terlipressin vasoconstriction?

A. Obtain central access
B. Order chest radiograph
C. Measure oxygen saturation
D. Order computed tomography (CT) of the head

The correct answer is: C (Measure oxygen saturation)

Answer rationale:

- Within the CONFIRM trial, a higher incidence of respiratory failure was observed with terlipressin treatment as compared to placebo (13.5% vs 5%). It is hypothesized that this may be caused by pulmonary edema due to the mechanisms of terlipressin influencing hydrostatic pressure, oncotic pressure, and the permeability of vascular endothelium.
- Due to these observed results, oxygen saturation should be measured prior to the first dose of terlipressin.
- If a patient is experiencing hypoxia, it is recommended that terlipressin not be initiated until the hypoxia resolves.
- A chest X-ray or CT of the head is not required prior to the administration of terlipressin for treatment of HRS-AKI.
- Terlipressin may be administered through a peripheral or central line. A dedicated central line is not required for the administration of terlipressin.

Faculty Commentary

Dr. Subramanian: Question 7 addresses the importance of monitoring for side effects when somebody is on vasoconstrictor therapy of terlipressin. The correct answer here is option C (measure oxygen saturation). This speaks to the potential risk of developing hydrostatic pulmonary edema when you are administering terlipressin. The latest randomized, controlled CONFIRM trial performed in North America did demonstrate efficacy of terlipressin with respect to HRS reversal, as previous trials did; but it also had a safety signal with respect to the development of clinically significant hypoxemia. As alluded to before by Dr. Nanchal, one of the mechanisms of how that may be happening is as you administer terlipressin and shut off the splanchnic shunt, you can actually increase MAP. That can increase your cardiac afterload. Also, you can have an increase in cardiac preload because you're decreasing the splanchnic shunt. A combination of increasing your afterload and preload can predispose these patients to the development of hydrostatic edema, which may become even more magnified if they have underlying diastolic heart dysfunction because of cirrhotic cardiomyopathy. An important take-home point is monitoring the pulmonary status before you start terlipressin initiation, as this question talks about. If somebody's hypoxemic, it would be a good idea to tease it out a bit more, such as getting a chest radiograph (chest X-ray) or if you have the luxury of getting an echocardiogram (echo) to see if they have any diastolic or systolic dysfunction. Those could be potential barriers to think about starting terlipressin. That may be an indication where you think about an alternative therapy, like norepinephrine or midodrine and octreotide.

Dr. Nanchal: Wonderful points and explanation. From my perspective, one of the things that our audience should probably know is that although pulmonary edema is a form of respiratory failure and severe hypoxemia are feared complications of terlipressin therapy, one shouldn't forget about other vasoconstrictor effects, especially in the digital and the mesenteric beds. Older people especially who may have atherosclerotic disease are prone to these effects as well.

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Clinical Endpoints for Vasoconstrictor Treatment in HRS-AKI

Question 8

Which one of the following is consistent with guideline recommendations on the clinical endpoints for vasoconstrictor titration?

A. Titrate norepinephrine continuous infusion for mean arterial pressure (MAP) >65 mmHg
B. Titrate norepinephrine continuous infusion for MAP ≥20 mmHg from baseline
C. Titrate terlipressin from 1 mg to 2 mg intravenous bolus every 6 hours for MAP ≥10 mmHg from baseline
D. Titrate terlipressin from 1 mg to 2 mg intravenous bolus every 6 hours if serum creatinine has not improved by 25%

The correct answer is: D (Titrate terlipressin from 1 mg to 2 mg intravenous bolus every 6 hours if SCr has not improved by 25%)

Answer rationale:

- The 2021 AASLD practice guidance defines a response to terlipressin or norepinephrine as a decrease in serum creatinine to <1.5 mg/dL or return to baseline within 0.3 mg/dL over a maximum of 14 days.
- The 2021 AASLD practice guidance and 2024 ADQI/ICA consensus meeting mutually recommend the titration of norepinephrine continuous infusion for an increase in MAP >10 mmHg from baseline or increase in UO >200 mL/4 hours or 50 mL/h for 4 hours.
- Previous studies demonstrate the magnitude of MAP rise with norepinephrine treatment correlates to an improved response, often measured by SCr reduction.
- The 2024 ADQI/ICA consensus meeting recommends the titration of terlipressin from 1 mg to 2 mg intravenous bolus every 6 hours if the serum creatinine has not improved by 25%.
- It is not recommended for terlipressin to be titrated to a MAP goal for use in the treatment of HRS-AKI.

Faculty Commentary

Dr. Nanchal: Question 8 pertains to the clinical endpoints of vasoconstrictor therapy in general. The correct answer is option D (titrate terlipressin from 1 mg to 2 mg intravenous bolus every 6 hours if SCr has not improved by 25%). There is some data in nations outside of the US to suggest terlipressin might work better as a continuous infusion because of its pharmacokinetic properties. This question gets into some really important points as to how do you know when to titrate the dose, and what to follow, as it is a little different for norepinephrine and terlipressin. As was alluded to before by Dr. Subramanian, when starting norepinephrine as the vasoconstrictor, we are usually targeting a MAP of about 10 to 15 mmHg above baseline. For most people, that will be about a MAP of 75 mmHg. For terlipressin, we are not targeting blood pressure, but rather looking at improvements in renal perfusion. The easiest way to measure that is the improvement in SCr and urine output, but mainly SCr. That is what we are looking at.

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Discontinuation of Vasoconstrictor Treatment in HRS-AKI

Question 9

Which one of the following is consistent with guideline-directed criteria for discontinuation of vasoconstrictor therapy?

A. Return of serum creatinine within 50% of baseline value
B. Lack of kidney function improvement after 24 hours of maximum tolerated dosing
C. Return of serum creatinine within ≤0.3 mg/dL of baseline value
D. Maximum of 10 days of therapy

The correct answer is: C (Return of serum creatinine within ≤0.3 mg/dL of baseline value)

Answer rationale:

- Criteria for discontinuation of vasoconstrictor therapy include return of kidney function to a baseline range, intolerance, occurrence of an adverse event, lack of kidney function response on maximum tolerated doses, or an indication for renal replacement therapy (RRT).
- The 2024 ACQI/IDA consensus meeting recommends discontinuation of vasoconstrictor treatment for HRS-AKI based on one of the following criteria:
    - SCr returns to within 0.3 mg/dL of baseline
    - Development of serious adverse reaction
    - Kidney function does not improve after 48h on maximum tolerated doses
    - Indication for RRT
    - Maximum of 14 days of therapy
- The 2021 AASLD practice guidance recommends discontinuation of vasoconstrictor treatment if the serum creatinine remains at or above the pretreatment level over 4 days with maximum tolerated doses.

Faculty Commentary

Dr. Nanchal: Question 9 pertains to the guideline-directed criteria for the discontinuation of vasoconstrictor therapy. The correct answer is option C (return of SCr within <0.3 mg/dL of baseline value). This is the criteria that was used in the largest trial to date of terlipressin, which was the CONFIRM trial. The other guideline-directed criteria is when there is resolution of HRS-AKI. We also have to be cognizant about continuously monitoring for adverse events on this therapy. Therapy can be discontinued if people develop severe adverse events, such as respiratory failure, kidney function deteriorates to the point of requiring dialysis, or something else happens that requires the therapy to be discontinued.

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Postdischarge Follow-Up in HRS-AKI

Question 10

Which one of the following post-discharge follow-ups would be most appropriate for this 68-year-old man with HRS-AKI successfully managed with guideline-recommended therapy?

A. Weekly monitoring of kidney and liver function for the first month after hospital discharge
B. Referral to a nephrology care provider for monitoring of kidney function
C. Referral for kidney transplant evaluation
D. Hepatology-nephrology consultation based on the severity of liver and kidney disease

The correct answer is: D (Hepatology-nephrology consultation based on the severity of liver and kidney disease)

Answer rationale:

- Patients with cirrhosis discharged after an episode of AKI remain at an increased risk for recurrence of AKI, progression to chronic kidney disease (CKD), dependence on dialysis, and mortality.
- The nature of liver and kidney recovery remains variable among patients who recover from HRS-AKI. Due to this, the 2024 ACQI/IDA consensus meeting recommends hepatology-nephrology consultation based on the severity of liver and kidney disease.
- Kidney function monitoring from a primary care provider may be an option for patients with less severe AKI or the return of kidney function to baseline following HRS-AKI. The frequency of monitoring may be at their discretion.
- A kidney-liver health (KLH) assessment is recommended within 1 month of discharge for surveillance measures and targeted prevention strategies following an AKI-inducing event. A KLH assessment consists of 5 domains, including education, medication management, disease-modifying interventions, and dynamic transplant and palliative care evaluations.
- KLH assessment may mitigate future risk of AKI to inform the susceptibility to AKI, nephrotoxin stewardship, and liver-specific recommendations for anticipated and unanticipated exposures.

Faculty Commentary

Dr. Subramanian: Question 10 addresses postdischarge follow-up after someone has received therapy for HRS-AKI. The correct answer is option D (hepatology-nephrology consultation based on the severity of liver and kidney disease). Important take-home point number 1 is that treatment with vasoconstrictor therapy for HRS-AKI will take care of the acute issue; but, there is a significant likelihood of return of that pathophysiology, so these patients are at risk for developing subsequent HRS-AKI which can then progress to hepatorenal syndrome-chronic kidney disease (HRS-CKD) and the need for dialysis. It is very important to have a multidisciplinary approach to the follow-up of these patients; the ideal state is evaluating that patient for liver transplantation, which is the only permanent solution to reversal of this physiology. Ideally, the patient will be assessed for liver transplantation and hopefully will not have any barriers from a surgical or medical comorbidity standpoint, for example. Just on that theme, it also speaks to the important physiologic concept about liver transplantation. Once the new liver goes in, that eliminates the underlying pathophysiology of splanchnic vasodilation and portal hypertension and, therefore, reverses the negative effects of splanchnic vasodilation on the systemic circulation. An important point remembering is that the ultimate fix, if you will, for HRS-AKI is successful liver transplantation.

The other point to be made is just reiterating the importance of a multidisciplinary approach. The ideal state is to have a hepatologist and a nephrologist working closely with the patient's primary care physician in order to take care of that patient post HRS-AKI therapy with terlipressin.

References

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Final Thoughts from the Faculty

Dr. Subramanian: Dr. Nanchal, as an intensivist, I was curious to get your input as far as how would you think about norepinephrine vs terlipressin options when you see a patient with HRS-AKI and the pros and cons of each strategy.

Dr. Nanchal: Great question, Ram, and I think you and I probably have very similar thoughts on this. So, A, administration of norepinephrine requires central venous access. The administration of terlipressin obviously doesn't, so it makes it a very attractive option of doing this out on the general medical ward where a lot more people can have access and can be performed easily. The dose is every 6 hours. I think the second point to be made is that whether we like it or are averse to it, a lot of people wind up in the ICU when their ACLF has worsened, and so the grade of ACLF prohibits the use of terlipressin in the ICU for the most part. I'm not saying that there are conditions and situations where you would not use it, but if you look at the probability of the patient being in the ICU and receiving terlipressin, it is not as high as someone getting it out on the floor. Those are the people that are sort of stuck doing norepinephrine. Thirdly, because it is a newer drug here in the US (but been out for decades), people are sort of hesitant to use terlipressin with even slight hypoxemia and things of that nature. And so, that is where I think we have seen some of the use of norepinephrine in lower grades of ACLF or, as you've mentioned, midodrine and octreotide. We prefer to do, whenever we can, norepinephrine over midodrine and octreotide. Even if they're not candidates for terlipressin, we will try and sort of get people into the ICU to do norepinephrine. Those are my thoughts. Because this is a conundrum, I'm curious to know your thoughts and how you approach this.

Dr. Subramanian: Those are great points. Just to add on to your comments, an important take-home point for the treatment of HRS-AKI is diagnose early and treat early. There's great data that if you diagnose early, as early as stage 2, defined as the doubling of a baseline SCr, you will have greater efficacy when you start vasoconstrictor therapy with terlipressin in respect to HRS-AKI reversal as opposed to waiting until your SCr is 4-5 mg/dL. In fact, SCr >5 mg/dL is a contraindication to even starting therapy. That speaks to the point about diagnosing early, and then the greatest option in treating early is outside of the ICU on the floor. That's the ideal state is to start the therapy (eg, when your SCr goes from let's say a baseline of 1 mg/dL and you identify the patient with HRS-AKI when their SCr is 2 mg/dL). I think that's where the sweet spot is with respect to initiating therapy. The other thing, as you mentioned, the logistics include treatment on the floor through a peripheral vein, lack of required central access, or finding an ICU bed for norepinephrine. That's the ideal state. I think you and I find ourselves in some of these tertiary care center phenotypes where patients get referred late, so they're already in advanced stage AKI with other extrarenal organ dysfunction issues that require ICU care. I think in those patient phenotypes in which they may already have a central line, you have the option of thinking about norepinephrine as an alternative to terlipressin, especially if you've got a contraindication to terlipressin, like hypoxemia.

Dr. Nanchal: Just as a follow-up, Ram, do you think that the newer criteria in the latest iteration from the 2024 ADQI/ICA consensus meeting will lead to earlier recognition and initiation of treatment for HRS-AKI?

Dr. Subramanian: That's a great point. I hope so. I think it has really changed the paradigm for us with respect to diagnosing HRS-AKI. As you know, we were waiting for a SCr of 2.5 mg/dL in the older criteria, which is way too late because their baseline SCr may have been 0.3-0.4 mg/dL. You're only looking at maybe stage 3 AKI. So, I think, as you just suggested, the newer guidelines that emphasize the doubling of the baseline SCr is an important trigger point to think about as vasoconstrictor therapy gives us an opportunity to really make a difference with respect to reversing HRS-AKI.